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Short Communication

Pterin Chemistry, Part 91. Synthesis and Crystal Structure of the First Molybdenum (IV)-q-dihydro-L-Biopterin Complex[1)]

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Introduction

Several oxidoreductases need molybdenum as a cofactor which, in association with a coenzyme, is the active center of these enzymes.

Now it is well established that most of them do not exhibit a fluorescence in their natural state, while they turn fluorescent as soon as they are denatured or oxidized. Furthermore we know that the origin of the fluorescence is the oxidized coenzyme, called *molybdopterin* because it is a C(6)-substituted pterin, which might be the same for all molybdenum-enzymes or, at least, nearly similar. Unfortunately none of the proposed structures for this coenzyme have been proven by synthesis. The coenzyme(s) must occur as reduced pterin(s) in the natural and active enzymes (For a review of the matter see (2)).

We have studied with 6β-5,6,7,8-tetrahydro-L-biopterin[3)] (BH_4) as a model compound the possible bonds existing between Mo and the reduced coenzymes in the molybdenum enzymes.

25 years ago we were faced with a similar problem, when we studied the reaction mechanism of the phenylalanine hydroxylase. The coenzyme of this enzyme is (BH_4) and the cofactor Fe(III). We demonstrated with a N(5)-methyltetrahydropterin derivative as a model substance, that two pterin molecules formed a brown colored complex with one Fe(III) ion. This complex activates molecular oxygen which, in consequence, oxidizes the tetrahydropterin (4).

Results and Discussion

In a similar manner $MO^{VI}O_2Cl_2$ reacts with BH_4 and forms a nearly quantitative dark red complex with a characteristic UV spectrum, corresponding to a reduced pterin plus a new maximum at 487 nm.

Crystallization of the complex was possible and the crystal structure could be solved by by X-ray diffraction (Fig. 1). The complex crystallizes in the noncentrosymmetric orthorhombic space group $P2_12_12_1$

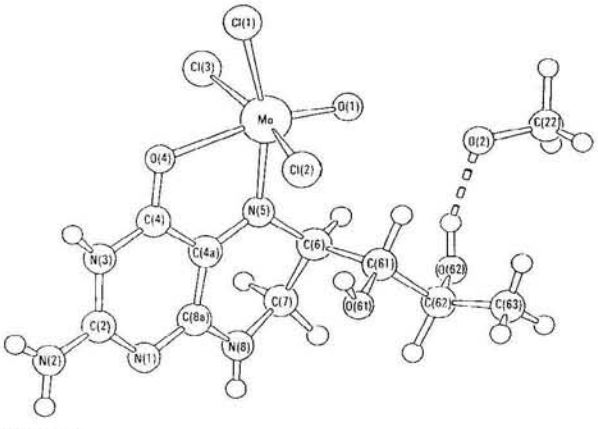

Figure 1.

[1)] Part 90 (1)

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[3)] We used for the hydropterins the consequent and unequivocal nomenclature proposed by us (3). According to CIP-rules the stereochemistry of this substance has to be described as 6R,1'R,2'S.

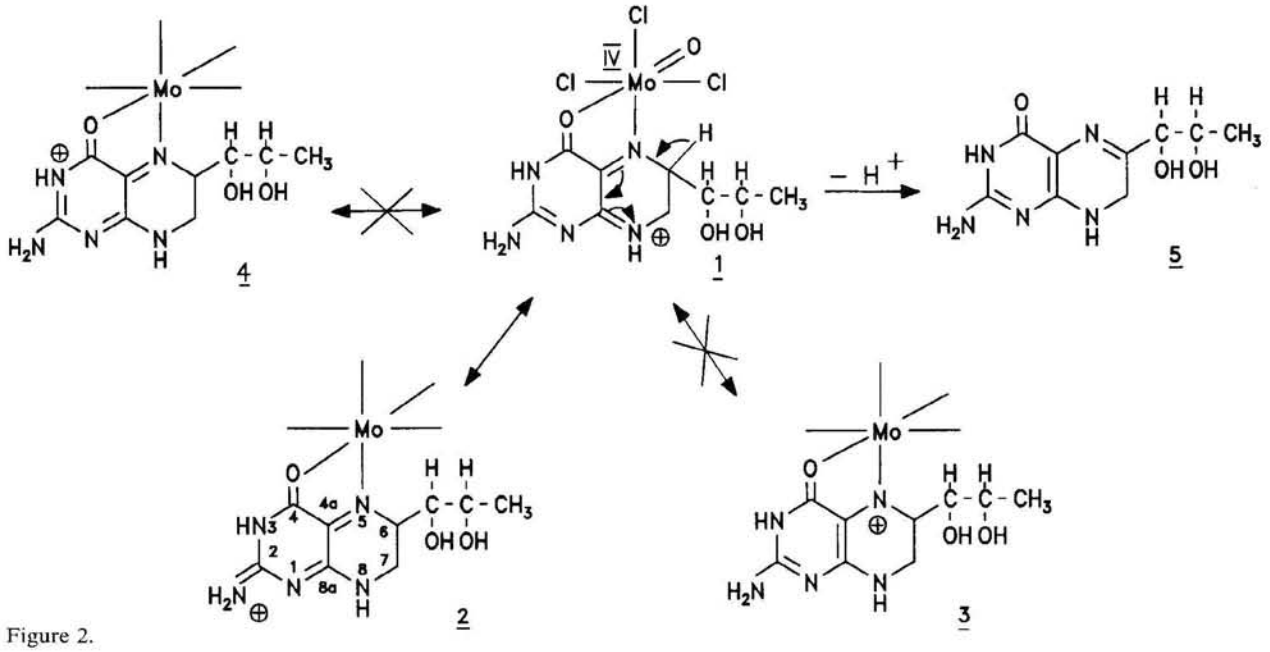

Figure 2.

(Nr. 19) with unit cell dimensions a = 1009,3(3) pm, b = 1104,7(3) pm, c = 1484,5(4) pm and Z = 4. The molybdenum atom has a distorted octahedral geometry. It is coordinated by N(5) and O(4) of the pterin ligand. The distance of the Mo-N(5) bond (202 pm) is unusually short compared to similar complexes. O(4) is located trans to a terminal oxo ligand. The octahedral coordination is completed by three chlorine atoms in a *meridional* arrangement.

The obtained data demonstrated that BH_4 was partially oxidized to a quinonoid derivative with the possible mesomeric structures *1*, *2*, *3* and *4* (Fig. 2). An analysis of the bond lengths shows similar distances of 132-134 pm between the atoms N(2)-C(2)-N(1)-C(8a)-N(8) indicating that the mesomeric structures *1* and *2* are the predominant species.

The distance of the C(4a)-C(8a) bond is 143 pm and the mesomeric system *1* ↔ *3* can therefore be excluded.

The clearly found proton at the N(3)-atom and the long bond distance of 139 pm for N(3)-C(2) rules out an endocyclic 7,8-dihydro(6H)biopterin form *4* with a N(3)–C(2) double bond (*1* ↔ *4*). An endocyclic 7,8-dihydro(6H)biopterin tautomer has been proposed by several authors to be reduced to BH_4 by dihydropteridine reductase [DHPR (human)] (5, 6, 7).

In solution the quinonoid structure *1* may be preferable in the mesomeric system *1* ↔ *2*, because it favours the well known 7,8-dihydro rearrangement *1* ↔ *5* by a facile deprotonation. The complex therefore could be formulated as N(2)–N(8)-mesomeric trichloro(6β-quinonoid-6,7-dihydro(8H)-L-biopterin) oxomolybdenum(IV).

The complex, dissolved in methanol, slowly forms an equilibrium with the initial reactants:

$$Mo^{VI}O_2Cl_2 + BH_4 \cdot 2\,HCl \xrightarrow{\text{Methanol}}$$

$$\xrightarrow{\text{Methanol}} Mo^{IV}OCl_3(\text{H-quinonoid})BH_2 + H_2O + HCl\uparrow$$

$$Mo^{IV}OCl_3(\text{H-quinonoid})BH_2 + CH_3OH \rightleftharpoons$$

$$\rightleftharpoons Mo^{VI}OCl_3(OCH_3) + BH_4$$

This could be demonstrated by ^{13}C-NMR spectroscopy. For the first time it could be shown that a quinonoid-dihydrobiopterin might be converted to a tetrahydrobiopterin in the presence of a transition metal.

This complex, with the molybdenum in the enzyme-relevant oxidation state + IV should lead to an extension of the proposed *common molybdenum cofactor* model. In the reduced form of the cofactor the molybdenum atom should be coordinated by a quinonoid 7,8-dihydro(6H)pterin.

The tables of the bond distances and angles, the experimental and the ^{13}C-NMR data were published in Helvetica Chimica Acta (1).

Acknowledgements

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